DESCRIPTION

Sugar intake-ability enhancer

5   Technical field

The present invention relates to a pharmaceutical
composition containing as an active ingredient one or more
HMG-CoA reductase inhibitor(s) for enhancement of glucose
uptake into warm-blooded animal cells; enhancement of
10   glucose uptake into warm-blooded animal cells in the
presence of insulin; treatment of diabetes, hyperglycemia,
glucose intolerance or gestational diabetes mellitus;
treatment or prevention of diabetes complications
(including retinopathy, nephropathy, neuropathy, cataract
15   and coronary artery disease); and treatment or prevention
of diabetes, hyperglycemia, glucose intolerance,
gestational diabetes mellitus or diabetes complications
(including retinopathy, nephropathy, neuropathy, cataract
and coronary artery disease) caused by insulin resistance
20   syndrome, and,

a method comprising administration of an effective
amount of one or more HMG-CoA reductase inhibitor(s) to a
warm-blooded animal for enhancement of glucose uptake into
warm-blooded animal cells; enhancement of glucose uptake
25   into warm-blooded animal cells in the presence of insulin;
treatment of diabetes, hyperglycemia, glucose intolerance
or gestational diabetes mellitus; treatment or prevention
of diabetes complications (including retinopathy,
nephropathy, neuropathy, cataract and coronary artery
30   disease); and treatment or prevention of diabetes,
hyperglycemia, glucose intolerance, gestational diabetes
mellitus or diabetes complications (including retinopathy,

nephropathy, neuropathy, cataract and coronary artery disease) caused by insulin resistance syndrome.

Background art

5   Blood glucose level is primarily determined by the balance between the uptake of glucose in peripheral tissues such as muscle and fat and the production of glucose in the liver. Insulin, which is secreted from the pancreas according to the blood glucose level, maintains homeostasis
10   of blood glucose levels by promoting glucose uptake in these peripheral tissues and suppressing glucose production in the liver. When diabetes and so forth occurs caused by increased insulin resistance, the action of insulin weakens resulting in a disorder in the blood glucose level control
15   function. As a result, a state of elevated blood glucose continues resulting in glucotoxicity throughout the body, and severe hyperglycemia causes diabetes complications such as retinopathy and neuropathy. Medicaments that enhance glucose uptake in peripheral tissues have the action of
20   improving hyperglycemia by promoting glucose metabolism, and are useful for the treatment or prevention of diabetes, hyperglycemia, glucose intolerance, gestational diabetes mellitus or diabetes complications (Homko, C.J. et al., Diabetes, 2003, 52, 487-491; Giannoukakis, N. et al.,
25   Biodrugs, 2002, 16, 149-173).

       A disease state associated with increased insulin resistance, or so-called insulin resistance syndrome, is the major cause of diabetes, while also being considered to be the fundamental cause of lifestyle diseases including
30   circulatory diseases (arteriosclerosis, hypertension, etc.) and obesity (McVeigh, G.E. et al., Current Diabetes Reports, 2003, 3, 87-92; Chaudhuri, A. et al., Current Diabetes Reports, 2002, 2, 305-310; Sorisky, A. et al., American

Journal of Therapeutics, 2002, 9, 516-521). Insulin resistance is related to glucose uptake in peripheral tissues, and improvement of insulin resistance is known to promote glucose uptake in peripheral tissues (Vazquez, M.

5   et al., Methods & Findings in Experimental & Clinical Pharmacology, 2002, 24, 513-523). Thus, medicaments that enhance glucose uptake in peripheral tissues by acting on the function of insulin to improve insulin resistance are useful for the treatment or prevention of diabetes,

10   hyperglycemia, glucose intolerance, gestational diabetes mellitus or diabetes complications caused by insulin resistance syndrome.

Although certain types of quinone compounds or nucleic acid derivatives have been known to demonstrate glucose

15   uptake enhancing action in cells of peripheral tissues (for example, Zhang, B. et al., Science, 1999, 284, 974-977; Merill, G.F. et al., American Journal of Physiology, Endocrinology and Metabolism, 1997, 273, E1107-E1112, and so forth), HMG-CoA reductase inhibitors have not been known

20   to demonstrate glucose uptake enhancing action on warm-blooded animal cells.

HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase inhibitors are well-known hyperlipemia therapeutic medicaments (for example, US Patent No. 4346227 et al.).

25   Statins are typical HMG-CoA reductase inhibitors, and disease preventive effects in humans have been confirmed in various clinical studies. For example, pravastatin has been reported to demonstrate effects (preventive effects) that suppress the onset of arteriosclerosis, coronary

30   artery disease and diabetes in a clinical study targeted at hyperlipemia patients (for example, MacMahon, S. et al., Circulation, 1998, 97, 1784-1790; Shepherd, J. et al.,

Lancet, 2002, 360, 1623-1630; Freeman, D.J. et al., Circulation, 2001, 103, 357-362; etc.).

However, HMG-CoA reductase inhibitors are not known to demonstrate therapeutic effects for diabetes, hyperglycemia, glucose intolerance or gestational diabetes mellitus as well as therapeutic or preventive effects for diabetes complications.

Disclosure of the invention

The inventors of the present invention found that an HMG-CoA reductase inhibitor has superior glucose uptake enhancing action on warm-blooded animal cells, and is useful as a pharmaceutical composition for enhancement of glucose uptake into warm-blooded animal cells; enhancement of glucose uptake into warm-blooded animal cells in the presence of insulin; treatment of diabetes, hyperglycemia, glucose intolerance or gestational diabetes mellitus; treatment or prevention of diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease); and treatment or prevention of diabetes, hyperglycemia, glucose intolerance, gestational diabetes mellitus or diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease) caused by insulin resistance syndrome, thereby leading to completion of the present invention.

The present invention provides a pharmaceutical composition comprising as an active ingredient one or more HMG-CoA reductase inhibitor(s) for enhancement of glucose uptake into warm-blooded animal cells; enhancement of glucose uptake into warm-blooded animal cells in the presence of insulin; treatment of diabetes, hyperglycemia, glucose intolerance or gestational diabetes mellitus;

treatment or prevention of diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease); and treatment or prevention of diabetes, hyperglycemia, glucose intolerance,

5 gestational diabetes mellitus or diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease) caused by insulin resistance syndrome, and,

a method comprising administration of an effective

10 amount of one or more HMG-CoA reductase inhibitor(s) to a warm-blooded animal for enhancement of glucose uptake into warm-blooded animal cells; enhancement of glucose uptake into warm-blooded animal cells in the presence of insulin; treatment of diabetes, hyperglycemia, glucose intolerance

15 or gestational diabetes mellitus; treatment or prevention of diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease); and treatment or prevention of diabetes, hyperglycemia, glucose intolerance, gestational diabetes

20 mellitus or diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease) caused by insulin resistance syndrome.

The present invention is:

(1) a pharmaceutical composition for enhancement of glucose

25 uptake into warm-blooded animal cells comprising as an active ingredient one or more HMG-CoA reductase inhibitor(s);

(2) a pharmaceutical composition for enhancement of glucose uptake into warm-blooded animals cells in the presence of

30 insulin comprising as an active ingredient one or more HMG-CoA reductase inhibitor(s);

(3) a pharmaceutical composition as (1) or (2), wherein the HMG-CoA reductase inhibitor is a medicament selected from

the group consisting of pravastatin, lovastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, pitavastatin and rosuvastatin;

(4) a pharmaceutical composition as (1) or (2), wherein the HMG-CoA reductase inhibitor is a water-soluble HMG-CoA reductase inhibitor;

(5) a pharmaceutical composition as (1) or (2), wherein the HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin and rosuvastatin;

(6) a pharmaceutical composition as (1) or (2), wherein the HMG-CoA reductase inhibitor is pravastatin;

(7) a pharmaceutical composition for the treatment of diabetes, hyperglycemia, glucose intolerance or gestational diabetes mellitus, or the treatment or prevention of diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease), comprising as an active ingredient one or more medicament(s) selected from the group consisting of pravastatin, lovastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, pitavastatin and rosuvastatin;

(8) a pharmaceutical composition for the treatment of diabetes, hyperglycemia, glucose intolerance or gestational diabetes mellitus caused by insulin resistance syndrome, or the treatment or prevention of diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease) caused by insulin resistance syndrome, comprising as an active ingredient one or more medicament(s) selected from the group consisting of pravastatin, lovastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, pitavastatin and rosuvastatin;

(9) a pharmaceutical composition for the treatment of diabetes, hyperglycemia, glucose intolerance or gestational diabetes mellitus, or the treatment or prevention of

diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease), comprising as an active ingredient one or more water-soluble HMG-CoA reductase inhibitor(s);

5　(10) a pharmaceutical composition for the treatment of diabetes, hyperglycemia, glucose intolerance or gestational diabetes mellitus caused by insulin resistance syndrome, or the treatment or prevention of diabetes complications (including retinopathy, nephropathy, neuropathy, cataract

10　and coronary artery disease) caused by insulin resistance syndrome, comprising as an active ingredient one or more water-soluble HMG-CoA reductase inhibitor(s);

(11) a pharmaceutical composition as (9) or (10), wherein the water-soluble HMG-CoA reductase inhibitor is a

15　medicament selected from the group consisting of pravastatin and rosuvastatin;

(12) a pharmaceutical composition as (9) or (10), wherein the water-soluble HMG-CoA reductase inhibitor is pravastatin;

20　(13) a method for enhancing glucose uptake into warm-blooded animal cells comprising administration of an effective amount of one or more HMG-CoA reductase inhibitor(s) to a warm-blooded animal;

(14) a method for enhancing glucose uptake into warm-

25　blooded animal cells in the presence of insulin comprising administration of an effective amount of one or more HMG-CoA reductase inhibitor(s) to a warm-blooded animal;

(15) a method as (13) or (14), wherein the HMG-CoA reductase inhibitor is a medicament selected from the group

30　consisting of pravastatin, lovastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, pitavastatin and rosuvastatin;

(16) a method as (13) or (14), wherein the HMG-CoA reductase inhibitor is a water-soluble HMG-CoA reductase inhibitor;

(17) a method as (13) or (14), wherein the HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin and rosuvastatin;

(18) a method as (13) or (14), wherein the HMG-CoA reductase inhibitor is pravastatin;

(19) a method for the treatment of diabetes, hyperglycemia, glucose intolerance or gestational diabetes mellitus, or the treatment or prevention of diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease), comprising administration of an effective amount of one or more medicament(s) selected from the group consisting of pravastatin, lovastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, pitavastatin and rosuvastatin to a warm-blooded animal;

(20) a method for the treatment of diabetes, hyperglycemia, glucose intolerance or gestational diabetes mellitus caused by insulin resistance syndrome, or the treatment or prevention of diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease) caused by insulin resistance syndrome, comprising administration of an effective amount of one or more medicament(s) selected from the group consisting of pravastatin, lovastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, pitavastatin and rosuvastatin to a warm-blooded animal;

(21) a method for the treatment of diabetes, hyperglycemia, glucose intolerance or gestational diabetes mellitus, or the treatment or prevention of diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease), comprising administration of

an effective amount of one or more water-soluble HMG-CoA reductase inhibitor(s) to a warm-blooded animal;

(22) a method for the treatment of diabetes, hyperglycemia, glucose intolerance or gestational diabetes mellitus caused

5   by insulin resistance syndrome, or the treatment or prevention of diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease) caused by insulin resistance syndrome, comprising administration of an effective amount of one or more water-

10   soluble HMG-CoA reductase inhibitor(s) to a warm-blooded animal;

(23) a method as (21) or (22), wherein the water-soluble HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin and rosuvastatin;

15   (24) a method as (21) or (22), wherein the water-soluble HMG-CoA reductase inhibitor is pravastatin; or

(25) a method as any one of (13) to (24), wherein the warm-blooded animal is a human.

There are no particular restrictions on the HMG-CoA

20   reductase inhibitor(s) serving as an active ingredient compound of the present invention provided it is a compound that demonstrates HMG-CoA reductase inhibitory action, examples of which include compounds having HMG-CoA reductase inhibitory action, pharmacologically acceptable

25   salts thereof, or pharmacologically acceptable esters thereof as described in Japanese Patent Application (Kokai) No. Sho 57-2240 (US Patent No. 4346227), Japanese Patent Application (Kokai) No. Sho 57-163374 (US Patent No. 4231938), Japanese Patent Application (Kokai) No. Sho 56-

30   122375 (US Patent No. 4444784), Japanese Patent Application (Kokai) No. Sho 60-500015 (US Patent No. 4739073), Japanese Patent Application (Kokai) No. Hei 1-216974 (US Patent No. 5006530), Japanese Patent Application (Kokai) No. Hei 3-

58967 (US Patent No. 5273995), Japanese Patent Application (Kokai) No. Hei 1-279866 (US Patent Nos. 5854259 and 5856336) or Japanese Patent Application (Kokai) No. Hei 5-178841 (US Patent No. 5260440), preferably pravastatin,

5   lovastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, pitavastatin or rosuvastatin, more preferably pravastatin or rosuvastatin, and most preferably pravastatin.

For an HMG-CoA reductase inhibitor serving as an

10   active ingredient compound of the present invention, a water-soluble HMG-CoA reductase inhibitor such as pravastatin and rosuvastatin is preferable. In the present invention, a water-soluble HMG-CoA reductase inhibitor is an HMG-CoA reductase inhibitor in which the logarithm of

15   the partition coefficient measured between phosphate buffer solution (pH 7.0 to 8.0, preferably pH 7.0 to 7.5, and more preferably pH 7.0) and 1-octanol [log(test substance concentration in 1-octanol phase/test substance concentration in buffer solution phase)] is 1.0 or less

20   (preferably 0.5 or less, and more preferably 0.0 or less) (McTaggart, F. et al., The American Journal of Cardiology, 2001, 87, 28B-32B; Chapman, M. J. et al., Atherosclerosis Supplements, 2002, 33-37; Shimada, Y. et al., Progress in Medicine, 1998, 18, 957-962). The aforementioned partition

25   coefficient can be measured according to ordinary methods (Partition Coefficient (n-octanol/water), OECD Guidelines for Testing of Chemicals, Section 1, Physical Chemical Properties, Paris, 1981, 107; Shimada, Y. et al., Progress in Medicine, 1998, 18, 957-962) or similar methods thereto.
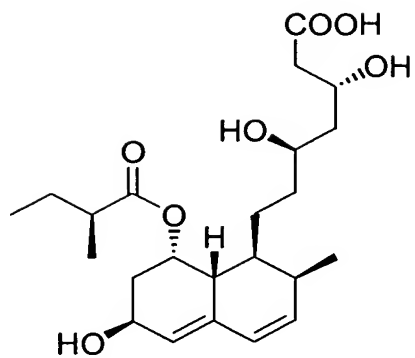
30   In addition, for an HMG-CoA reductase inhibitor serving as an active ingredient compound of the present invention, pravastatin or derivative thereof, or rosuvastatin or derivative thereof, is preferable. In the

present invention, a derivative of pravastatin is a
compound having HMG-CoA reductase inhibitory action, a
pharmacologically acceptable salt thereof or ester thereof
as described in Japanese Patent Application (Kokai) No. Sho

5   57-2240 (US Patent No. 4346227), while a derivative of
rosuvastatin is a compound having HMG-CoA reductase
inhibitory action, a pharmacologically acceptable salt
thereof or ester thereof as described in Japanese Patent
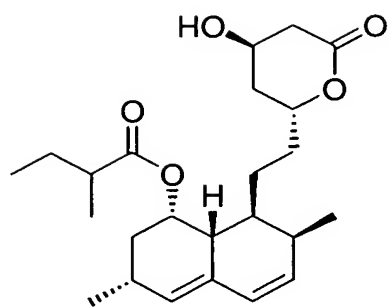Application (Kokai) No. Hei 5-178841 (US Patent No.

10   5260440).
     Pravastatin is (+)-(3R,5R)-3,5-dihydroxy-7-
[(1S,2S,6S,8S,8aR)-6-hydroxy-2-methyl-8-[(S)-2-
methylbutyryloxy]-1,2,6,7,8,8a-hexahydro-1-
naphthyl]heptanoic acid, and includes its pharmacologically

15   acceptable salts or esters (for example, monosodium salt of
the aforementioned pravastatin, etc.) as described in
Japanese Patent Application (Kokai) No. Sho 57-2240 (US
Patent No. 4346227). Lovastatin is (+)-(1S,3R,7S,8S,8aR)-
1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-

20   tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthyl
(S)-2-methylbutyrate, and includes its pharmacologically
acceptable salts or esters as described in Japanese Patent
Application (Kokai) No. Sho 57-163374 (US Patent No.
4231938). Simvastatin is (+)-(1S,3R,7S,8S,8aR)-

25   1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-
tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthyl
2,2-dimethylbutyrate, and includes its pharmacologically
acceptable salts or esters as described in Japanese Patent
Application (Kokai) No. Sho 56-122375 (US Patent No.

30   4444784). Fluvastatin is (±)-(3R*,5S*,6E)-7-[3-(4-
fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-
dihydroxy-6-heptenoic acid, and includes its
pharmacologically acceptable salts or esters (for example,

monosodium salt of the aforementioned fluvastatin, etc.) as described in Japanese Patent Application (Kokai) No. Sho 60-500015 (US Patent No. 4739073). Cerivastatin is (3R,5S,6E)-7-[4-(4-fluorophenyl)-2,6-di-(1-methylethyl)-5-

5 methoxymethylpyridin-3-yl]-3,5-dihydroxy-6-heptenoic acid, and includes its pharmacologically acceptable salts or esters (for example, monosodium salt of the aforementioned cerivastatin, etc.) as described in Japanese Patent Application (Kokai) No. Hei 1-216974 (US Patent No.

10 5006530). Atorvastatin is (3R,5S)-7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-phenylaminocarbonyl-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid, and includes its pharmacologically acceptable salts or esters (for example, 1/2 calcium salt of the aforementioned atorvastatin, etc.)

15 as described in Japanese Patent Application (Kokai) No. Hei 3-58967 (US Patent No. 5273995). Pitavastatin is (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropylquinolin-3'-yl]-6-heptenoic acid, and includes its pharmacologically acceptable salts or esters (for example, 1/2 calcium salt

20 of the aforementioned pitavastatin, etc.) as described in Japanese Patent Application (Kokai) No. Hei 1-279866 (US Patent Nos. 5854259 and 5856336). Rosuvastatin is (+)-(3R,5S)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)pyrimidin-5-yl]-3,5-dihydroxy-6(E)-

25 heptenoic acid, and includes its pharmacologically acceptable salts or esters (for example, 1/2 calcium salt of the aforementioned rosuvastatin, etc.) as described in Japanese Patent Application (Kokai) No. Hei 5-178841 (US Patent No. 5260440).
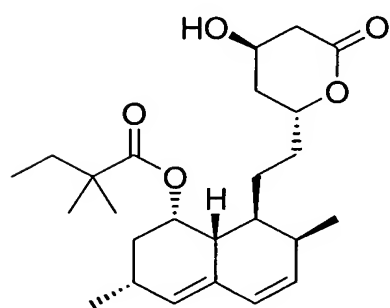
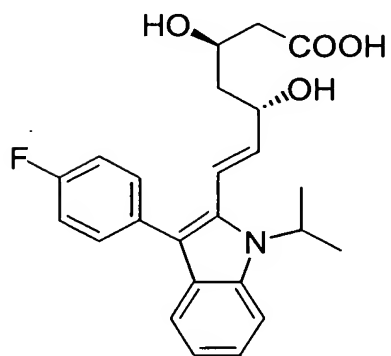30 The following indicates the two-dimensional structural formulas of major HMG-CoA reductase inhibitors.
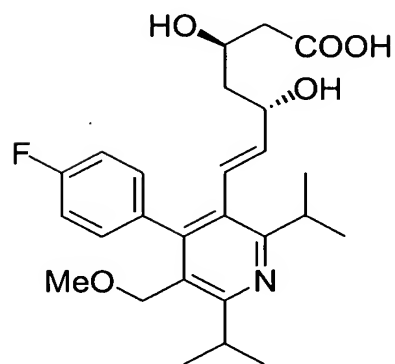
Pravastatin
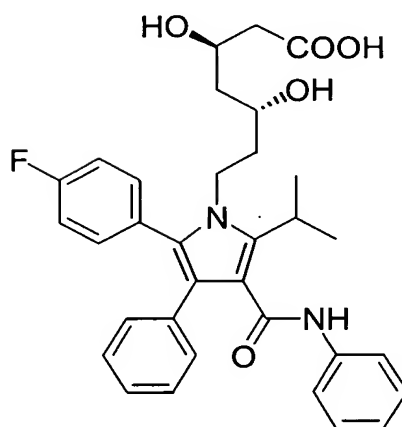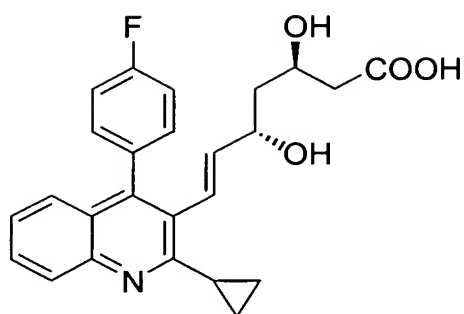
Lovastatin

Simvastatin

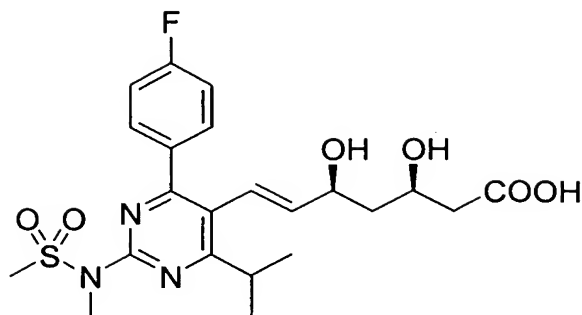Fluvastatin

Cerivastatin

Atorvastatin

Pitavastatin   Rosuvastatin

In the case where the aforementioned HMG-CoA reductase
inhibitor has an asymmetric carbon, all of its racemate,

5   its optical isomers and mixtures thereof are included in
the HMG-CoA reductase inhibitor of the present invention.
In addition, hydrates of the aforementioned HMG-CoA
reductase inhibitors are also included in the HMG-CoA
reductase inhibitor of the present invention.

10   For an HMG-CoA reductase inhibitor serving as an
active ingredient compound in the present invention, one
type of compound can be used alone, or a mixture of two or
more types of compounds can be used. In the case of using
a mixture of two or more types of compounds, the compounds

15   can be used simultaneously or each of compounds can be used
separately at different times.

An HMG-CoA reductase inhibitor serving as an active
ingredient of the present invention can easily be prepared
in accordance with known methods [for example, Japanese

20   Patent Application (Kokai) No. Sho 57-2240 (US Patent No.
4346227), Japanese Patent Application (Kokai) No. Sho 57-
163374 (US Patent No. 4231938), Japanese Patent Application
(Kokai) No. Sho 56-122375 (US Patent No. 4444784), Japanese
Patent Application (Kokai) No. Sho 60-500015 (US Patent No.

25   4739073), Japanese Patent Application (Kokai) No. Hei 1-
216974 (US Patent No. 5006530), Japanese Patent Application

(Kokai) No. Hei 3-58967 (US Patent No. 5273995), Japanese Patent Application (Kokai) No. Hei 1-279866 (US Patent Nos. 5854259 and 5856336), Japanese Patent Application (Kokai) No. Hei 5-178841 (US Patent No. 5260440), etc.] or similar methods thereto.

Industrial applicability

In the case of using the HMG-CoA reductase inhibitor(s) serving as an active ingredient of the present invention as a pharmaceutical (pharmaceutical composition for treatment or prevention of the aforementioned diseases), it can be administered in the form of a bulk medicament of the pharmaceutical itself; or it can be orally administered in a formulation such as tablet, capsule, granules, pill, powder, liquid, syrup, troche, suspension, emulsion, etc. or be parenterally administered in a formulation such as an injection, suppository or patch, etc., which formulations are made by mixing the HMG-CoA reductase inhibitor with a suitably pharmacologically acceptable excipient, binder and so forth. An oral administration is preferred.

These formulations are prepared using well-known methods using additives such as excipients, binders, disintegrants, lubricants, emulsifiers, stabilizers, corrigents, diluents, injection solvents and so forth.

An excipient may be, for example, an organic excipient or inorganic excipient. Examples of organic excipients include sugar derivatives such as lactose, sucrose, glucose, mannitol and sorbitol; starch derivatives such as cornstarch, potato starch, alpha starch, dextrin and carboxymethyl starch; cellulose derivatives such as crystalline cellulose, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, calcium carboxymethyl

cellulose, and internally-crosslinked sodium carboxymethyl cellulose; gum arabic; dextran; and, pullulan. Examples of inorganic excipients include silicic acid salt derivatives such as light anhydrous silicic acid, synthetic aluminium silicate, calcium silicate, and magnesium metasilicate aluminate; phosphoric acid salts such as calcium phosphate; carbonic acid salts such as calcium carbonate; and sulfuric acid salts such as calcium sulfate.

Examples of binders include the compounds as described for the aforementioned excipient; gelatin; polyvinylpyrrolidone; and, polyethylene glycol.

Examples of disintegrants include the compounds as described for the aforementioned excipient; chemically modified starch or cellulose derivatives such as crosscarmelose sodium and sodium carboxymethyl starch; and, crosslinked polyvinylpyrrolidone.

Examples of lubricants include talc; stearic acid; metal stearates such as calcium stearate and magnesium stearate; colloidal silica; waxes such as bee gum and spermaceti; boric acid; glycol; DL-leucine; carboxylic acids such as fumaric acid and adipic acid; carboxylic acid sodium salts such as sodium benzoate; sulfates such as sodium sulfate; lauryl sulfates such as sodium lauryl sulfate and magnesium lauryl sulfate; silicic acids such as anhydrous silicic acid and silicic acid hydrate; and the above starch derivatives as for the aforementioned excipients.

Examples of emulsifiers include colloidal clays such as bentonite and bee gum; metal hydroxides such as magnesium hydroxide and aluminium hydroxide; anionic surfactants such as sodium lauryl sulfate and calcium stearate; cationic surfactants such as benzalkonium chloride; and, nonionic surfactants such as polyoxyethylene

alkyl ether, polyoxyethylene sorbitan fatty acid ester, and sucrose fatty acid ester.

Examples of stabilizers include parahydroxybenzoic acid esters such as methyl paraben and propyl paraben;

5 alcohols such as chlorobutanol, benzyl alcohol or phenylethyl alcohol; benzalkonium chloride; phenols such as phenol and cresol; thimerosal; dehydroacetic acid; and sorbic acid.

Examples of corrigents include ordinarily used

10 sweeteners, sour flavourings, fragrances, etc..

Examples of diluents include water, ethanol, propylene glycol, ethoxyisostearyl alcohol and polyoxyethylene sorbitan fatty acid ester.

Examples of injection solvents include water, ethanol

15 and glycerin.

The HMG-CoA reductase inhibitor(s) serving as an active ingredient of the present invention can be administered to a warm-blooded animal (and particularly a human). The dose can be varied depending on various

20 conditions such as the symptoms and age of the patient. In the case of oral administration, 0.1 mg (preferably 0.5 mg) as a lower limit and 1000 mg (preferably 500 mg) as an upper limit can be administered once to six times per day for a human adult depending on the symptoms. In the case

25 of parenteral administration, 0.01 mg (preferably 0.05 mg) as a lower limit and 100 mg (preferably 50 mg) as an upper limit can be administered once to six times per day for a human adult depending on the symptoms.

Since the HMG-CoA reductase inhibitor(s) serving as an

30 active ingredient of the present invention has superior glucose uptake enhancing action in the presence or absence of insulin (preferably in the presence of insulin) in warm-blooded animal cells (preferably warm-blooded animal

adipocytes), it is useful as a pharmaceutical composition
for enhancement of glucose uptake into warm-blooded animal
cells (preferably warm-blooded animal adipocytes);
enhancement of glucose uptake into warm-blooded animal

5   cells (preferably warm-blooded animal adipocytes) in the
presence of insulin; treatment of diabetes, hyperglycemia,
glucose intolerance or gestational diabetes mellitus;
treatment or prevention of diabetes complications
(including retinopathy, nephropathy, neuropathy, cataract

10   and coronary artery disease); and treatment or prevention
of diabetes, hyperglycemia, glucose intolerance,
gestational diabetes mellitus or diabetes complications
(including retinopathy, nephropathy, neuropathy, cataract
and coronary artery disease) caused by insulin resistance

15   syndrome,
        preferably for enhancement of glucose uptake into
warm-blooded animal cells in the presence of insulin;
treatment of diabetes; treatment or prevention of diabetes
complications (including retinopathy, nephropathy,

20   neuropathy, cataract and coronary artery disease);
treatment of diabetes, hyperglycemia, glucose intolerance
or gestational diabetes mellitus caused by insulin
resistance syndrome; and treatment or prevention of
diabetes complications (including retinopathy, nephropathy,

25   neuropathy, cataract and coronary artery disease) caused by
insulin resistance syndrome,
        more preferably for enhancement of glucose uptake into
warm-blooded animal cells in the presence of insulin;
treatment of diabetes, hyperglycemia, glucose intolerance

30   or gestational diabetes mellitus caused by insulin
resistance syndrome; and treatment or prevention of
diabetes complications (including retinopathy, nephropathy,

neuropathy, cataract and coronary artery disease) caused by insulin resistance syndrome,

and even more preferably for enhancement of glucose uptake into warm-blooded animal cells in the presence of insulin; treatment of diabetes caused by insulin resistance syndrome; and treatment or prevention of diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease) caused by insulin resistance syndrome.

In addition, the aforementioned pharmaceutical composition is preferably for warm-blooded animals, and more preferably for humans. A pharmaceutical composition for treatment or prevention of the present invention is preferably a pharmaceutical composition for treatment.

Best mode for carrying out the invention

Although the following provides a more detailed explanation of the present invention by indicating Examples and Formulation examples, the scope of the present invention is not limited thereto.

(Example 1) Glucose uptake enhancing action (in vitro)
(1) Cell culturing

Preadipocyte cell line 3T3-L1 was purchased from the American Type Culture Collection (ATCC). The 3T3-L1 cells were plated onto a 24-well, collagen-coated plate and cultured to saturation in growth medium (DMEM, 25 mM glucose, 10% FCS, 100 u/ml penicillin, 0.1 mg/ml streptomycin) under conditions of 37°C and 5% CO_2. Five days after cell proliferation had reached a saturated state, the medium was replaced with medium (DMEM, 25 mM glucose, 10% FCS, 100 u/ml penicillin, 0.1 mg/ml streptomycin) to which had been added 1 µM insulin, 0.5 mM 3-isobutyl-1-

methylxanthine and 1 µM dexamethazone to initiate adipocyte differentiation. Two days later, the medium was replaced with growth medium containing 1 µM insulin followed by additionally culturing the cells for 2 days. Subsequently,

5   the medium was replaced with fresh growth medium every 3 days, and the 3T3-L1 adipocytes were prepared on day 10 after the start of differentiation.

Test compounds that were poorly soluble in water were used after dissolving in DMSO. Test compounds that were

10   easily soluble in water were dissolved in sterile water followed by addition of the same amount of DMSO as that used for the aforementioned poorly water-soluble test compounds. In addition, in the case of test compounds that are poorly soluble in water, the test compound may be

15   dissolved in ethanol and used following the addition of 0.1 N aqueous sodium hydroxide solution after shaking as necessary.

After allowing the 3T3-L1 cells to adequately differentiate into adipocytes, a test compound was added to

20   the medium to a final concentration of 10 µM followed by culturing the cells for 72 hours.

(2)   Measurement of glucose uptake

Following treatment with the test compound, the cells were washed with KRBH buffer solution (6.91 g/l NaCl, 0.37

25   g/l KCl, 0.30 g/l MgSO$_4$ · 7H$_2$O, 0.19 g/l CaCl$_2$ · 2H$_2$O, 0.21 g/l K$_2$HPO$_4$, 25 mM HEPES, 2 g/l NaHCO$_3$, 0.1% BSA (Sigma), 0.11 g/l sodium pyruvate, 100 u/ml penicillin, 0.1 mg/ml streptomycin) and then cultured for 3.5 hours at 37°C. Subsequently, insulin was added to the cells followed by

30   additionally culturing the cells for 30 minutes.

Measurement of glucose uptake was carried out in the manner described below. Namely, 0.1 µCi of ^{3}H-labeled 2-

deoxyglucose was added to the medium followed by removal of the medium ten minutes later and washing with phosphate buffer solution (phosphate-buffered saline: PBS, pH 7.4). After washing, 200 μl of 1 N aqueous sodium hydroxide

5   solution were added to the cells to lyse the cells. 160 μl of the cell lysate were mixed with 4 ml of Hionic Fluor (Perkin-Elmer) liquid scintillation counter cocktail followed by measurement of the radioactivity in the cell lysate with a liquid scintillation counter (Packard). The

10 determined radioactivity of the ^{3}H-labeled was used as an indicator of the amount of glucose taken up into the cells. The amount of glucose uptake into the cells was 1.9 times higher ($P<0.001$) in the group in which pravastatin was used for the test compound than in the control group.

15   According to this result, an HMG-CoA reductase inhibitor serving as an active ingredient of the present invention was determined to have superior action of enhancing glucose uptake into warm-blooded animal cells, and be useful as a pharmaceutical composition for

20 enhancement of glucose uptake into warm-blooded animal cells; enhancement of glucose uptake into warm-blooded animal cells in the presence of insulin; treatment of diabetes; treatment or prevention of diabetes complications (including retinopathy, nephropathy, neuropathy, cataract

25 and coronary artery disease); treatment or prevention of diabetes, hyperglycemia, glucose intolerance, gestational diabetes mellitus or diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease) caused by insulin resistance syndrome; etc..

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(Example 2) Glucose uptake enhancing action (in vivo)
(1)   Administration of Pravastatin to mice in feed
(i)   Test animals

C57BL/ksj-db/db mice (male, age 5 weeks) and KKAy mice (female, age 4 weeks) were purchased from Clea Japan, and used in the test after acclimating to the test environment for 1 week. The mice were housed 5 animals to a cage and given unrestricted access to feed (F2, Funabashi Farm) and water.

(ii) Schedule

The body weights of the animals were measured and blood samples were collected on the day the test started, and the animals were divided into two groups of 5 animals per cage based on their body weights and blood glucose levels. Blood samples were collected at the start of the test and days 4, 7 and 14 after the start of the test in the case of the C57BL/ksj-db/db mice, and at the start of the test and on days 4, 7, 14 and 28 after the start of the test in the case of the KKAy mice. Blood samples were collected from the tail vein in an amount equal to one heparinized capillary tube.

(iii) Administration method

Pravastatin powder was added to the F2 powder to 0.03% and 0.06% (wt/wt), uniformly mixed and provided to the animals in individual cages. The amount of feed and general behaviour were checked at least once a day.

(iv) Measurement

Blood glucose levels were measured on the days when blood samples were collected. The Glucose CII-Test Wako (Wako) was used for measurement of blood glucose levels.

(2) Insulin tolerance test using Pravastatin-dosed mice

A group administered with pravastatin by mixing in feed for 2 weeks and a non-dosed group of C57BL/ksj-db/db mice (n=5) were fasted for 2 hours. After measuring the body weight of each animal, insulin (Humalin, Lilly) was administered intraperitoneally at 1 u/kg, and blood samples

were collected from the tail vein immediately before the start of administration and at 30, 60, 90 and 120 minutes after the start of administration followed by measurement of blood glucose levels.

5   (3)   Glucose tolerance test using Pravastatin-dosed mice

A group administered with pravastatin by mixing in feed for 2 weeks and a non-dosed group of C57BL/ksj-db/db mice (n=5) were fasted for 16 hours starting on the day before the start of the test. After measuring the body

10   weight of each animal, glucose solution (0.5 g/l) was administered intraperitoneally to 2 g/kg, and blood samples were collected from the tail vein immediately before the start of administration and at 30, 60, 90 and 120 minutes after the start of administration followed by measurement

15   of blood glucose levels.

(4)   Glucose uptake test using isolated adipocytes from Pravastatin-dosed mice

(i)   Epididymal adipose tissue was excised from a group administered with pravastatin for 1 week and a non-dosed

20   group of C57BL/ksj-db/db mice (n=5). The excised adipose tissue was handled under conditions of 37°C at all times. The adipose tissue was cut into small pieces with a scissors, followed by the addition of medium (DMEM, 1 mM sodium pyruvate, 25 mM HEPES pH 7.4, 0.1% BSA, 100 u/ml

25   penicillin, 0.1 mg/ml streptomycin) containing 1 mg/ml of collagenase I (Worshington), and shaking at 37°C and 80 rpm. Following the reaction, 2.5 volumes of the aforementioned medium were added, the adipocytes were screened out by passing the cell suspension through a 260 μm mesh sieve,

30   and again passed through a 100 μm mesh sieve to prepare an adipocyte suspension.

An adipocyte suspension was prepared for C57BL/6J mice (normal mice) in the same manner as described above.

(ii) The glucose uptake test was carried out in the manner as described below. 100 µl of the aforementioned cell

5   suspension, 90 µl of medium and 10 µl of insulin solution were added to a polystyrene tube, while stirring gently to uniformly distribute the adipocytes in each tube, and the adipocytes cultured for 30 minutes at 30°C. Subsequently, 0.6 µCi of ^{3}H-labeled 2-deoxyglucose was added and allowed

10   to react for 30 minutes. Following the reaction, the cell suspension was immediately transferred to a centrifuge tube containing silicone oil and centrifuged. After cutting out the oil layer of the upper layer containing adipocytes with a knife, it was transferred to a glass vial containing 4 ml

15   of Hionic Fluor (Perkin-Elmer) liquid scintillation counter cocktail followed by measurement of specific radioactivity. The amount of measured radioactivity of the ^{3}H-2-deoxyglucose was used as an indicator of the amount of glucose taken up by the cells.

20   (5) Results

In (1) above, as a result of administering pravastatin to C57BL/ksj-db/db mice and KKAy mice serving as a model of obesity type 2 diabetes prior to the onset of diabetes, prominent inhibitory action on increases in blood glucose

25   levels was observed (C57BL/ksj-db/db mice: non-dose group 633 mg/dl, dose group 438 mg/dl; KKAy mice: non-dose group 521 mg/dl, dose group 351 mg/dl).

In the insulin tolerance test of (2) above, the pravastatin dose group demonstrated significantly lower

30   blood glucose levels than the non-dose group at 60 minutes after administration of insulin (non-dose group: 411 mg/dl, dose group: 324 mg/dl).

In the glucose tolerance test of (3) above, the pravastatin dose group demonstrated significantly lower blood glucose levels than the non-dose group at 60 minutes after administration of insulin (non-dose group: 517 mg/dl,

5   dose group: 342 mg/dl).

In the C57BL/6J mouse and C57BL/ksj-db/db mouse adipocytes in (4) above, the pravastatin dose group demonstrated increased insulin sensitivity and increased glucose uptake more than the non-dose group. In the

10 C57BL/6J mice, the amount of glucose uptake by the dose group was 1.4 times greater than that by the non-dose group, and in the C57BL/ksj-db/db mice, the amount of glucose uptake by the dose group was 2.0 times greater than that by the non-dose group.

15   From the aforementioned results, an HMG-CoA reductase inhibitor serving as an active ingredient of the present invention was determined to have superior action of enhancing glucose uptake into warm-blooded animal cells, and be useful as a pharmaceutical composition for

20 enhancement of glucose uptake into warm-blooded animal cells; enhancement of glucose uptake into warm-blooded animal cells in the presence of insulin; treatment of diabetes, hyperglycemia, glucose intolerance or gestational diabetes mellitus; treatment or prevention of diabetes

25 complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease); and, treatment or prevention of diabetes, hyperglycemia, glucose intolerance, gestational diabetes mellitus or diabetes complications (including retinopathy, nephropathy,

30 neuropathy, cataract and coronary artery disease) caused by insulin resistance syndrome.

(Formulation Example 1) Tablets

   After mixing 10 parts of pravastatin sodium, 71.55 parts of lactose, 20 parts of low substituted hydroxypropyl cellulose (LH21, Shin-Etsu Chemical), 20 parts of

5 crystalline cellulose (Avicel PH101, Asahi Kasei) and 6.5 parts of magnesium metasilicate aluminate (Neusilin FL2, Fuji Chemical Industry) with a Henschel mixer (Mitsui Mining), 13 parts of a 10% aqueous solution of hydroxypropyl cellulose (Nippon Soda) and a suitable amount

10 of water were added to the resulting mixture followed by kneading with a Henschel mixer. The resulting kneaded product was dried for 1 hour at 60°C with an air dryer. The resulting dried product was sized with a power mill (Dalton) equipped with a 1 mm φ diameter screen, and 129.65

15 parts of the resulting granules and 0.65 parts of magnesium stearate (NOF Corporation) were mixed with a V-mixer (Tokuju Seisakusho). The resulting mixture was formed into tablets to produce tablets having a diameter of 7.0 mm.